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# Is Deep Brain Stimulation (DBS) an Effective Treatment for Refractory Obsessive Compulsive Disorder (OCD) in Adults?

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# Is Deep Brain Stimulation (DBS) an Effective Treatment for Refractory Obsessive Compulsive Disorder (OCD) in Adults?

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Introduction

Obsessive-compulsive disorder (OCD) is a common psychiatric disorder, creating harmful effects on social and occupational functioning for OCD patients.. OCD is characterized by "persistent thoughts (obsessions) and repetitive ritualistic behaviors (compulsions)."[1] Common obsessions include contamination fears and forbidden sexual thoughts, while common compulsions include cleaning and counting rituals.[2] Many patients experience OCD symptoms beginning in childhood, leading to a chronic and debilitating disease when left untreated.[2] Currently, OCD has an estimated lifetime prevalence of 2%, affecting both genders equally.[1] In 1990 (the most recent year for which data is available), it was estimated that the total costs of OCD were 8.4 billion dollars;[3] this has likely gone up tremendously in the past two decades. In addition, from the years 1995-1996, 2,043 individuals from a 1,728,480 person health maintenance organization (HMO) had the clinical diagnosis of OCD.[4]

Currently, the exact cause of OCD is unknown, however at this time it has been thought that the cause is due to a combination of genetic and environmental factors.[5] With many studies underway, "recent evidence highlights an abrupt onset of OCD symptoms in some cases in the context of group A beta-hemolytic streptococcal (GABHS) infection."[5] With specific disease causes largely unknown, treatment is often generalized in nature.[5] Common conventional treatments are pharmacotherapy with high-dose serotonergic antidepressant medications or behavioral psychotherapy, or a combination of the two[5]. Despite treatment advances, it is estimated that current treatments provide a "mean of 40% to 60% symptom reduction in half of the patients," leaving many with ongoing symptoms.[1] In addition, 10% of patients will be plagued with severe, treatment-refractory OCD.[1] For a portion of treatment-refractory patients, neurosurgical treatment may serve as a more effective, long-lasting resort.

Deep brain stimulation (DBS) is a neurosurgical treatment in which electrodes are implanted in specific areas of the brain, selected according to the type of symptoms being targeted.[1] The electrodes send out electrical impulses to the neuronal tissue of the target brain location.[1] Although not widely used, DBS is promising in that it may provide an alternate treatment option for refractory OCD, with successful outcomes having already been shown.

Objective

The objective of this systematic review is to determine whether or not deep brain stimulation (DBS) is an effective treatment for refractory obsessive compulsive disorder (OCD) in adults.

Methods

All three studies included in this review met the following criteria. The population included adults at least 18 years of age with treatment refractory OCD and a minimum score of 25 on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS).[1,6,7] The Abelson et al[6] and Denys et al[1] studies were both double-blind, sham-controlled randomized controlled trials, while the third study used, Goodman et al[7], was a blinded, staggered-onset randomized controlled trial. The intervention used was deep brain stimulation of the following areas of the brain: ventral anterior limb of the internal capsule and adjacent ventral striatum (Goodman et al[7]), nucleus accumbens of the ventral striatum (Denys et al[1]), and the anterior limb of each internal capsule (Abelson et al[6]). All studies reviewed compared the treatment group to a control group which received random "sham stimulation."[1,6,7] The main outcome measured in each of the studies was the severity of OCD symptoms based on changes from baseline in OCD symptoms using Y-BOCS.[1,6,7] This outcome qualifies as patient oriented evidence that matters (POEM).

The author searched for articles using PubMed, Medline and Cochrane Databases using the keywords "obsessive-compulsive disorder," "refractory," and "deep brain stimulation." All

articles selected were published in English, in peer-reviewed journals. The inclusion criteria were studies that were randomized controlled trials published after 1996 and that had patient-oriented outcomes (POEMS). The exclusion criteria were articles that included patients under the age of 18 years old, patients that were diagnosed with substance abuse, or lastly, patients that were diagnosed with psychoses. The statistics included were p-values and Numbers Needed to Treat (NNT).

Table 1: Demographics and Characteristics of Included Studies

| Study | Type | # Pts | Age | Inclusion Criteria | Exclusion Criteria | W/D | Interventions |
|---|---|---|---|---|---|---|---|
| Denys et al[1] | Double-blind, sham-controlled RTC | 16 | 21-59 | Pts. diagnosed with primary OCD using DSM-IV, ≥28 on Y-BOCS, >5 year history of OCD, exp substantial functional impairment according to DSM-IV Criterion C, GAF score of 45 or less, experienced refractoriness to therapy, partook in at least 1 CBR for ≥16 sessions | Pts. who had clinically significant DSM-IV comorbid diagnoses, who had severe personality disorders, who had clinically significant and unstable neurologic or medical illnesses | 2 | Treatment with bilateral DBS of the nucleus accumbens |
| Abelson et al[6] | Double-blind, sham-controlled RCT | 4 | 27-52 | Patients who had a Y-BOCS scale ≥25, a GAF score less than 44, who had multiple unsuccessful treatment attempts with anti-obsessional mediation, who partook in medication trials on at least four anti-obsessional medications proven effective, who had exposure to various medication combinations, who received 12 weeks of CBT w/o meaningful benefit and who were in "good" general health | Pts. who had no history of psychosis and who has no current substance abuse | N/A | Quadripolar stimulating electrodes placed stereotaxically in the anterior limb of each internal capsule; connected via subcutaneous wires to implantable pulse generators placed in the subclavicular area |
| Goodman et al[7] | Blinded, staggered-onset RCT | 6 | 27-52 | Patients who met DSM-IV score for OCD, ≥28 on Y-BOCS, 5-year history of treatment refractory OCD symptoms since age 18, partook in an adequate trial of clomipramine, and at least two SSRIs (fluoxetine, fluvoxamine, citalopram, sertraline, paroxetine), with addition of one or more of the aforementioned drugs with at least two of the following: clonazepam, haloperidol, | Patients who had a lifetime diagnosis of psychosis or bipolar disorder, who had chemical abuse issues within the previous six months, who had a primary diagnosis of depression within the previous year, who had a current DSM-IV Axis II diagnosis from cluster A, and | N/A | Treatment with DBS electrode arrays placed bilaterally in an area spanning the ventral anterior limb of the internal capsule and adjacent ventral striatum. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | risperidone, olanzapine or gabapentin and who partook in an adequate trial of CBT | who had the presence of brain pathology | | |

Outcomes Measured

Each article's primary outcome measured was OCD symptom severity based on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). The Y-BOCS is a clinician rated scale with 10 different items scored from either 0 (no symptoms) to 40 (severe symptoms).[8] This scale has questions dealing with both obsessions and compulsions. The scores then represent a stage of OCD, with a score of 0-7 indicating subclinical OCD, 8-15 as mild OCD, 16-23 as moderate OCD, 24-31 as severe OCD and 32-40 as extreme OCD.[8] Goodman et al[7] specified that each Y-BOCS assessment was conducted by either the principle investigator, a clinical psychiatrist, or a psychiatric research nurse, Denys et al[1] specified that assessments were conducted by a trained investigator; however, Abelson et al[6] failed to specify who conducted the assessments.

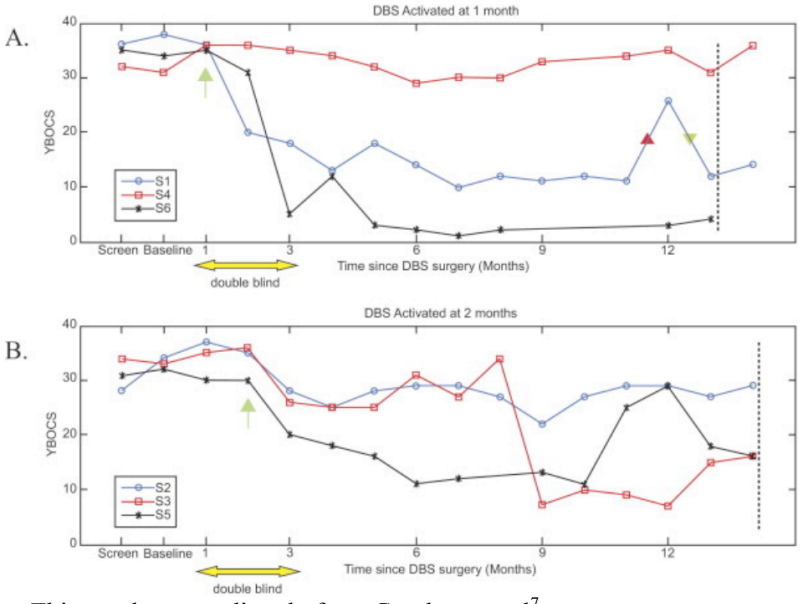
Each study also assessed secondary outcome measures such as the Hamilton Depression Scale (HAM-D) and the Hamilton Anxiety Scale (HAM-A). This review is limited to results based on the severity of OCD symptoms using the Y-BOCS assessment.

Results

In Goodman et al[7], a responder was defined as a subject with both a 35% reduction in score from baseline and an actual Y-BOCS score of 16 or less at the time of assessment. This definition of a responder created a set of dichotomous data; responders and non-responders. Y-BOCS scores were also analyzed as continuous data with repeated-measure analysis of variance (ANOVA).[7] All six of the study's participants were implanted with neuro-stimulation. At one month post-implantation, three of the subjects received active DBS while the remainder of the subjects received sham stimulation.[7] At two months, those receiving sham stimulation were converted to active DBS.[7] At this two month mark, all study participants were receiving active

DBS[7]. All of the above actions were conducted in a double blind setting. Graph 1[7] demonstrates Y-BOCS score progression over time, with 1A demonstrating the scores of the early DBS activation group and 1B demonstrating the scores of the late DBS activation group. It is important to note that unbeknownst to subject 1 or the treatment team, subject 1's right-sided battery was depleted between 11 and 12 months.[7] The ineffective DBS battery led to an OCD exacerbation (black triangle) and then a subsequent normalization (gray triangle) shortly after battery replacement[7].

Graph 1. Y-BOCS Score vs. Time Since DBS Surgery




a. This graph comes directly from Goodman et al[7]

Visual inspection of Graph 1[7] demonstrates very little reduction in Y-BOCS scores with the control subjects (sham stimulation) and an obvious varying decrease in Y-BOCS scores upon DBS activation. Overall, there was a significant decrease in Y-BOCS scores over time, with a decrease of 15.67 ± 11.60 after 12 months of DBS activation (p-value of 0.0392 using ANOVA).[7] Four of the six participants were classified as responders. The RBI and ABI were calculated to be 67% with NNT being 2 patients, as demonstrated in Table 2[7].

Table 2. Key Values from the Three RCT's Being Reviewed

| | p-value | CER | EER | RBI | ABI | NNT |
|---|---|---|---|---|---|---|
| Goodman et al[7] | 0.0392 | 0% | 67% | 67% | 67% | 2 patients |
| Abelson et al[6] | N/A | 0% | 25% | 25% | 25% | 4 patients |
| Denys et al[1] | 0.004 | 0% | 56% | 56% | 56% | 2 patients |

Overall, the Goodman et al[7] study was relatively safe, with all original participants completing the trial in its totality. Compliance was not specifically noted, however it is assumed that actual DBS compliance was 100% being that stimulators were neuro-surgically implanted, with no indication that the DBS stimulation was removed throughout the trial. It is important to note that unexpected adverse events did not occur in response to implantation, such as seizures or cerebral hemorrhage.[7] Table 3 demonstrates the adverse events of stimulation observed throughout the trial. Only one serious event was noted upon which hospitalization was required[7].

Table 3. Goodman et al[7] Adverse Events

| Adverse Event | N | % Affected |
|---|---|---|
| Contralateral smile w/ mirth | 5 | 83.333% |
| Hypomania | 4 | 66.667% |
| Serious AE (unspecified, but required hospitalization) | 1 | 16.667% |
| Bipolar Disorder | 0 | 0.000% |

In Abelson et al[6], a responder was defined as one who experienced ≥ 35% decline in Y-BOCS score from baseline. According to Abelson et al[6], "the literature indicates that the anterior capsulotomy produces a 35% improvement in OCD symptoms in about 45% of patients who receive the operation,"[6] hence the justification of this study's responder definition. It is important to note that an exploratory phase of the study was performed prior to the double-blind phase. During this phase, which was performed at a General Clinical Research Center, a range of stimulation parameters were tested to determine tolerability and effects of stimulation.[6] This exploratory phase helped determine evidence of stimulation benefit and/or "maximum levels of undetectable sitmulation."[6]

In the double-blind phase of this study (the only phase being analyzed in this review), one out of four subjects were classified as responders. Throughout the double-blind study, there were a total of eight ON periods (active stimulation) and eight OFF periods (sham stimulation).[6] As seen in Table 3, Subject 3 (responder) demonstrated a 67% reduction in Y-BOCS score from baseline during the ON periods, while only demonstrating a 23% reduction in Y-BOCS score from baseline during the OFF periods.[6] Subject 2 (non-responder) demonstrated a 13% change from baseline during ON stimulation and a 19% change from baseline during OFF stimulation, demonstrating some sort of placebo effect.[6] The mean reduction from baseline in Y-BOCS with stimulators ON was 19.8% (SD 29.8), while the mean with stimulators OFF was 10.5% (SD 17.8).[6] As Table 2 demonstrates, the NNT was 4 patients (the entire subject population for this study).

Table 3. Abelson et al[6] Subject Characteristics and Mean Y-BOCS Scores during Double Blind Testing

| | **Subject 1** | **Subject 2** | **Subject 3** | **Subject 4** |
|---|---|---|---|---|
| Age | 52 | 27 | 48 | 34 |
| OCD Duration (years) | 46 | 11 | 16 | 17 |
| Gender | Male | Female | Female | Male |
| Symptoms | Repeating, reentering, order/symmetry, counting | Intrusive images (of sex, violence), mental arranging, counting, cleaning | Contamination, cleaning, checking/repeating, symmetry | Repeating, "just right" behavior |
| Baseline Y-BOCS Score | 39 | 36 | 30 | 26 |
| Mean (% decline in Y-BOCS from baseline)—ON | 37.5 (4) | 31.5 (13) | 10 (67) | 27 (-4) |
| Mean (% decline in Y-BOCS from baseline)[a]—OFF | 39 (0) | 29 (19) | 23 (23) | 26 (0) |
| Side Effects of Stimulation | None | Throbbing, buzzing, nausea, diarrhea | Tingling | Jaw sensations |

a. All information from this table was taken directly from Abelson et al[6]

Also seen in Table 3 are the DBS side effects that each of the four subjects experienced in the Abelson et al[6] study. Somatic symptoms such as throbbing, buzzing, nausea, diarrhea, tingling and jaw sensations were noted.[6] Overall, no evidence of cognitive impairment or personality changes were noted from either patients or family members.[6] Despite side effects, there was a 100% retention rate of study subjects throughout the double-blind phase of the trial.[6]

Similar to Abelson et al[6], in the study performed by Denys et al[1], responders were defined as those with a ≥ 35% decrease in Y-BOCS score from baseline. Prior to the double-blind, sham controlled phase of the Denys et al[1] study, there was an open stimulation phase. This open DBS phase lasted 8 months, with subjects being evaluated every 2 weeks for OCD symptom severity and optimal stimulation parameters.[1] At the conclusion of the 8 months, the double-blind, sham-controlled phase began. Subjects were randomly assigned two periods of 2 weeks each, with active stimulation in one period and sham stimulation during the other period.[1] Subjects were assessed at baseline, after their first 2 week period of either active or sham stimulation, and then after the second 2 week period.[1] It should be noted that two subjects refused to enter the double-blind, sham controlled crossover phase of experimentation. One subject feared losing the positive effects of open-phase DBS and the other was dissatisfied with the overall effects of DBS.[1] No further analysis was performed on these subjects. Overall there was a decrease in Y-BOCS score from baseline throughout the 8-month open stimulation phase, as demonstrated in Table 4. Mean scores during ON/OFF periods, as well as changes between ON and OFF periods during the double-blind phase were calculated, as demonstrated in Table 4 as well. The mean Y-BOCS score decrease from sham to active stimulation in the entire sample of 14 subjects was 8.8 points (SD of 9.1; 95% CI, 3.6-14.1; P.003).[1] After a correction for

period effects, stimulation "caused a substantial (mean, 8.3 [2.3] points [25%]) and statistically significant (P=.004) reduction in the Y-BOCS total score during the double-blind phase."[1]

As seen in Table 2, the NNT was calculated to be 2 patients. It is important to note that there were 9 responders out of 16 total subjects; however, the number of responders was calculated at the conclusion of the entire 21 month study. The double-blind crossover phase was followed by a 12 month maintenance phase, in which all participating subjects received active stimulation.[1] Also crucial to the results is the fact that for all but 4 subjects, the blinded status of the stimulator was lifted due to abrupt worsening of symptoms.[1]

Table 4. Denys et al[1] Changes in OCD Symptom Severity During Double-Blind Crossover Period

| Variable | Mean Baseline (SD) | After 8 mos of Stimulation (SD) | Start of Crossover Period | | Change Between Weeks 1-2 and Weeks 3-4 | |
|---|---|---|---|---|---|---|
| | | | Weeks 1-2 | Weeks 3-4 | Mean (SD) [95% CI] | P Value |
| Group 1 (n=6) Y-BOCS Total Score | 34.2 (3.6) | 23.3 (9.9) | After Stimulation On: 25.8 (9.3) | After Stimulation Off: 30.7 (4.5) | 4.9 (7.6) [-12.9 to 3.2] | .18 |
| Group 2 (n=8) Y-BOCS Total Score | 33.4 (3.6) | 18.7 (10.6) | After Stimulation Off: 29.5 (11.4) | After Stimulation On: 17.6 (10.1) | 11.9 (9.3) [4.0 to 19.7] | .009 |

a. All information from this table was taken directly from Denys et al[1]

In the Denys et al study[1], two of the sixteen total subjects refused to enter the double-blind phase of the study and only completed the open phase. Out of the remaining fourteen subjects, ten individuals requested the blinded status of the stimulation was lifted due to worsening of symptoms, as previously stated. An array of adverse events were reported and these can be split into surgery related, device related and stimulation related events. Issues such as infection at the incision site and numbness at the incision site were just a sample of the adverse events reported from surgery, with none of these being permanent.[1] Feelings of electrical current around the neurostimulator and feelings of the neurostimulator in the chest were device-related complaints reported by subjects, with some being permanent.[1] Lastly,

twenty-two different stimulation related effects were reported, with hypomanic symptoms being the most common complaint.[1] A few of these complaints, such as forgetfulness, were reported to be permanent.[1]

Discussion

Many previous studies have been done concerning the effects of deep brain stimulation on movement disorders, such as Parkinson's Disease. DBS for Parkinson's Disease has become much more wide-spread and accessible throughout the past decade.[9] Contrastingly, DBS and its effects on psychiatric disorders, such as OCD, is a much less familiar territory in terms of research and practice. In 2009, the FDA approved the "Medtronic Reclaim DBS therapy," which is "indicated for bilateral stimulation of the anterior limb of the internal capsule" for "severe, treatment-resistant obsessive compulsive disorder (OCD)."[10] The FDA also issued a warning of the potential danger of excessive DBS causing damage to neuronal tissue, which is a truly significant concern that all clinicians and patients must take into account.[10] The FDA guidelines are very specific, indicating DBS *only* for the anterior limb of the internal capsule, an area of the brain not even studied in Goodman et al[7].[10] Not only are indications for DBS in OCD sparse, but so is the availability of such a treatment. Most DBS procedures for OCD are performed only at major academic hospitals in large metropolitan areas. In addition, Medicare does cover DBS as a treatment for OCD; however, many private insurance companies do not.[11]

The limitations to each of the three studies being reviewed are numerous, and much more research must be carried out before DBS takes the place of anterior capsulotomy for the treatment of refractory OCD. Currently, anterior capsulotomy is the most prevalent, neurosurgical "last-resort" option for this illness and it is with hope that DBS will eventually be more successful than invasive capsulotomy.[12] Each of the three studies reviewed contained no

more than 20 subjects to analyze, a sample size that is significantly small for research and statistical analysis purposes. Also, the desperation of the subjects being studied and the last-resort context of DBS created a "fertile context for placebo responses."[6] In addition, many of the subjects developed a sense of the stimulator being ON vs OFF through a perceived somatic sensation.[6] This sense could have muffled the blind nature of the studies. In one study, the majority of subjects even refused to allow the blind status to be continued. Much more focus must also be put on finding the optimal stimulation parameters for an individual because this has the ability to greatly influence outcome.

Conclusion

The studies reviewed demonstrate inconclusive evidence as to whether or not deep brain stimulation (DBS) is an effective treatment for refractory obsessive-compulsive disorder (OCD) in adults. The Goodman et al[7] study is the only study that concluded that DBS is a "promising therapy of last resort for carefully selected cases of severe and intractable OCD."[7] Denys et al[1] and Abelson et al[6] admit to its potential, but are weary of widespread use without intense further research. In the future it would be advantageous to greatly improve the actual stimulator engineering in order to dissolve variables such as battery life and function. Also, more strict DBS parameters must be explored before the widespread use of DBS in refractory OCD. In addition, studies comparing anterior capsulotomy to DBS for the treatment of refractory OCD would be enlightening to this field of research.

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